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Serum platelet-derived growth factor BB levels: a potential biomarker for the assessment of liver fibrosis in patients with chronic hepatitis B

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SUMMARY

Objectives: Few studies have investigated serum levels of platelet-derived growth factor (PDGF) in patients with chronic hepatitis B (CHB). The present study aimed to determine whether PDGF-BB could serve as a potential biomarker for the detection of liver fibrosis.
Methods: From October 2013 to August 2015, 465 patients with CHB were enrolled prospectively in this study. All patients underwent liver biopsy and staging based on the Ishak system. The serum PDGF-BB level was measured quantitatively by ELISA.
Results: The serum PDGF-BB level was negatively correlated with fibrosis stage in all patients ($p = 0.003$, Spearman's rho = −0.16) and was significantly different between fibrosis stages. The areas under the receiver operating characteristics curves (AUROCs) for serum PDGF-BB level and PGT score (a combination of PDGF-BB, gamma-glutamyl transpeptidase, and platelet levels) were 0.667 and 0.831, respectively, for patients with significant fibrosis and normal alanine aminotransferase (ALT) levels. The AUROCs for aspartate aminotransferase-to-platelet ratio (APRI) and fibrosis index based on four factors (FIB-4) were 0.823 and 0.821, respectively. Importantly, a cut-off value of 1.05 and 1.43, respectively, resulted in a sensitivity of 0.95 and 0.52, a specificity of 0.29 and 0.95, a positive predictive value of 0.30 and 0.79, and a negative predictive value of 0.96 and 0.86. The rate of correct diagnosis was up to 88.4% when using cut-offs of 1.05 and 1.43 for the absence or presence of significant fibrosis, respectively.
Conclusions: Serum PDGF-BB decreased remarkably as fibrosis progressed, and this could be used as a non-invasive biomarker for the assessment of fibrosis stage in patients with CHB.

1. Introduction

Hepatitis B virus (HBV) infection remains a major global health concern. Approximately 240 million individuals are chronically infected with HBV worldwide, and 650 000 people die annually from HBV-related cirrhosis, hepatocellular carcinoma (HCC), and liver failure.[1,2] China has the world's largest burden of HBV infection, with an estimated 120 million people carrying hepatitis B surface antigen (HBsAg) and nearly 300 000 deaths from HBV-related liver disease each year.[3] Therefore, the assessment of liver pathology is very important clinically, as it identifies those patients who are most likely to benefit from therapeutic strategies.[4]

To date, percutaneous liver biopsy followed by histological analysis remains the main technique for evaluating the severity of liver injury. However, the clinical use of this diagnostic technique is limited by the invasiveness of the procedure and its associated drawbacks, including pain, bleeding, and sampling error.[5,6] Recently, several non-invasive methods and scoring models have been developed to assess liver damage.[7] Among these, the

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aspartate aminotransferase-to-platelet ratio (AST/PLT ratio; APRI) and fibrosis index based on four factors (FIB-4) have become the two most commonly used scoring methods; these were initially used to evaluate patients with chronic hepatitis C virus (HCV) infection.[8] A number of studies have indicated that APRI and FIB-4 are also appropriate markers for detecting liver fibrosis in patients with chronic hepatitis B (CHB) infection.[9,10] Furthermore, the most recent study to date, reported by the present study group, has established a fibrosis index (fib-index) for the assessment of liver fibrosis based on panels of selected cytokines.[11] Compared with APRI and FIB-4 scores, this fib-index showed greater diagnostic performance in identifying significant fibrosis in patients with mildly elevated alanine aminotransferase (ALT) levels.

It has been established that, in addition to cytokines, growth factors and other locally produced mediators govern the progression from chronic liver injury to fibrosis, cirrhosis, and eventually tumor formation. Platelet-derived growth factor (PDGF) belongs to a family of growth factors that were originally identified as key mediators of vascular pathologies.[12] Several recent studies have indicated that PDGF, one of the most potent known mitogens, promotes liver fibrosis by activating hepatic stellate cells (HSCs). Furthermore, PDGF is overexpressed in liver tissue during fibrogenesis.[13–15] However, few studies have investigated serum levels of PDGF in patients with liver fibrosis.

The aims of the current study were to evaluate the association between serum PDGF-BB level and histological liver damage in a large cohort, and to assess the diagnostic value of PDGF as a biomarker of liver fibrosis in patients with CHB.

2. Methods

2.1. Patients

From October 2013 to August 2015, 489 consecutive patients with CHB who underwent liver biopsy in 24 teaching hospitals located in mainland China were recruited into this study. Patients were included in the study if they met the following criteria: (1) HBsAg-positive for at least 6 months, (2) treatment-naïve, (3) aged between 18 and 65 years, (4) serum negative for anti-hepatitis A virus (HAV) IgM, anti-HCV, anti-hepatitis E virus (HEV) IgM/IgG, anti-Epstein–Barr virus (EBV) IgM, and anti-cytomegalovirus (CMV) IgM, and (5) no use of potential transaminase-lowering agents such as bicyclol for at least 2 weeks prior to blood sampling biochemistries. The exclusion criteria for this study encompassed overlapping etiologies for hepatitis, including HCV, hepatitis D virus (HDV), human immunodeficiency virus (HIV), alcoholism, autoimmune disease, genetic conditions, drug-induced liver disease, non-alcoholic fatty liver disease, and other chronic liver diseases. Patients with decompensated cirrhosis or HCC were also excluded.

All patients provided written informed consent for the scientific use of their clinical data and samples, and the study was approved by the local ethics committee of Peking University First Hospital. The complete protocol for the clinical trial has been registered at clinicaltrials.gov (NCT01962155) and chictr.org (ChiCTR-DDT-13003724).

2.2. Liver pathology

Ultrasonography-guided liver biopsies measuring ≥2.0 cm were routinely performed at each hospital according to a standardized protocol after receiving the patient's written informed consent. Pathological interpretations were conducted in the Department of Pathology at Youan Hospital, which is affiliated with the Capital Medical University. Each section was assessed independently and in a blinded fashion by two pathologists. When discrepancies in these assessments occurred, the samples were reviewed by experienced pathologists, who were also responsible for reassessing a random selection of 10% of the samples. Fibrosis was staged according to the Ishak fibrosis score, and a score of F≥3 was considered significant fibrosis.[8,16]

2.3. Examination of virological markers

Qualitative assessments of hepatitis B e antigen (HBeAg) and hepatitis B e antibody (HBeAb) levels were performed using relevant Roche Elecsys assays (Roche Diagnostics, Penzberg, Germany). Serum HBV DNA levels (range 2.0×10^1 to 1.7×10^8 IU/ml) were measured using a COBAS AmpliPrep/COBAS TaqMan method, as described previously.[17]

2.4. Determination of serum PDGF-BB level

The serum PDGF-BB level was determined using an ELISA (R&D, Minneapolis, MN, USA), according to the manufacturer's instructions.

2.5. APRI and FIB-4 scores

APRI and FIB-4 scores were calculated using the following formulas: APRI = (AST/upper limit of normal/PLT count (10^9/l)) × 100; FIB-4 = (age × AST)/(PLT count (10^9/l) × $ALT^{1/2}$).

2.6. Statistical analysis

All statistical analyses were performed using SPSS v.16.0 software (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as the mean ± standard deviation (SD). The Chi-square test was used to analyze relationships between categorical variables. The Student *t*-test, Kruskal–Wallis test, and Mann–Whitney *U*-test were used to analyze differences in normally and non-normally distributed variables between the groups. Spearman's rank tests were used to analyze associations between different variables and fibrosis stages. Multiple ordered analysis among variables was performed to derive independent related factors of fibrosis stages, and an algorithm for significant fibrosis was chosen. Another algorithm of parameters for significant fibrosis was also derived from logistic linear analysis. The diagnostic abilities of different variables were evaluated based on estimated areas under the receiver operating characteristics curve (AUROCs) and by calculations of the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of different cut-off points. Statistical significance was defined as $p < 0.05$ (two-tailed).

3. Results

3.1. Patient characteristics

A total of 489 patients were enrolled in this study; 24 patients were excluded (21 patients had no biopsy data and three patients had missing clinical data). The remaining 465 cases were analyzed, including 235 patients from the previous study by this group of authors.[11] Baseline characteristics of the study patients are summarized in Table 1.

3.2. Serum PDGF-BB decreased in parallel with fibrosis progression

Serum PDGF-BB was detected using ELISA kits. In the total CHB patient sample, the measured serum PDGF-BB levels differed significantly between fibrosis stages (F2 vs. F3, $p = 0.008$; F2 vs. F4, $p = 0.0001$; F2 vs. F5–6, $p = 0.008$; F3 vs. F5–6, $p = 0.001$; F4 vs. F5–6, $p = 0.003$) (Figure 1A). In the group of CHB patients with normal

Table 1
Patient characteristics[a]

Parameters	Total (n = 465)	ALT < ULN (n = 122)	ALT ≥ULN (n = 343)	p-Value[b]
Age ≥30 years	97 (20.9%)	23 (18.9%)	74 (21.6%)	0.31
Sex, male	363 (78.1%)	89 (73.0%)	274 (79.9%)	0.073
BMI, kg/m^2	23.35 ± 3.39	22.90 ± 2.76	23.52 ± 3.58	0.17
PDGF-BB, $\log_{10}$ pg/ml	4.75 ± 0.40	4.70 ± 0.40	4.77 ± 0.39	0.057
HBV DNA, $\log_{10}$ IU/ml	6.31 ± 1.89	5.74 ± 2.13	6.52 ± 1.759	<0.001
Platelet count, ×10^9/l	173.51 ± 53.68	176.13 ± 51.93	172.57 ± 58.35	0.54
AST, U/l	68.82 ± 90.15	26.06 ± 7.97	84.17 ± 100.68	<0.001
ALP, U/l	84.11 ± 28.71	74.45 ± 22.93	87.58 ± 29.80	<0.001
GGT, U/l	57.33 ± 63.59	32.00 ± 34.08	66.42 ± 69.07	<0.001
TBil, μmol/l	16.93 ± 15.72	14.50 ± 7.72	17.80 ± 17.67	0.009
Albumin, g/l	44.25 ± 5.36	44.63 ± 4.17	44.11 ± 5.72	0.283
PT, s	13.36 ± 6.77	12.78 ± 1.57	13.58 ± 7.84	0.263
INR	1.14 ± 1.52	1.03 ± 0.09	1.19 ± 1.80	0.15
Fibrosis stage				0.001
F0–1	148 (31.8%)	57 (46.7%)	91 (26.5%)	
F2	150 (32.3%)	33 (27.0%)	117 (34.1%)	
F3	90 (19.4%)	17 (13.9%)	73 (21.3%)	
F4	64 (13.8%)	14 (11.5%)	50 (14.6%)	
F≥5	13 (2.8%)	1 (0.85)	12 (3.5%)	

ALT, alanine aminotransferase; ULN, upper limit of normal; BMI, body mass index; PDGF-BB, platelet-derived growth factor BB; HBV, hepatitis B virus; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; TBil, total bilirubin; PT, prothrombin time; INR; international normalized ratio.
[a] Results are presented as the mean ± standard deviation, or n (%).
[b] Between patients with ALT <ULN (n = 122) and ALT ≥ULN (n = 343).

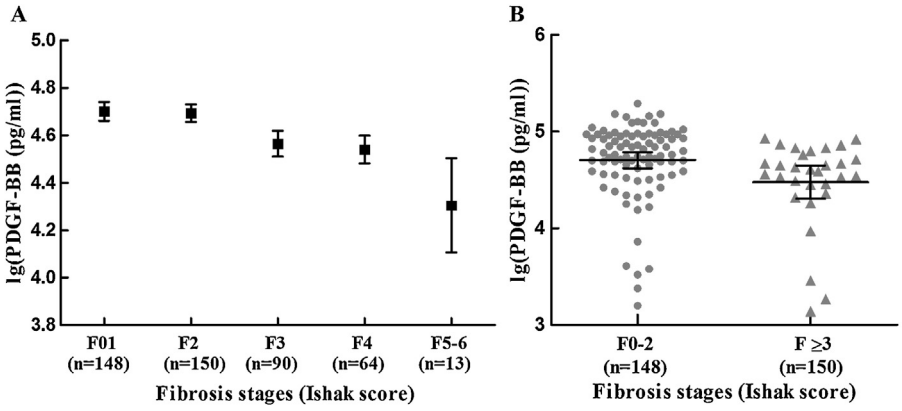

Figure 1. Serum platelet-derived growth factor BB (PDGF-BB) level correlated with histological fibrosis stages in (A) all chronic hepatitis B patients, and (B) chronic hepatitis B patients with normal alanine aminotransferase (ALT). Median values with the 95% confidence interval (of the median) are presented.

ALT, the patients with significant fibrosis had lower serum PDGF-BB levels than the patients with no significant fibrosis (F0–2 vs. F3–6, p = 0.0008) (Figure 1B). Spearman's rank test results showed that the serum PDGF-BB level was negatively correlated with fibrosis stage (p = 0.003, r = −0.16) in all patients. Correlational analyses indicated that the serum PDGF-BB level was clearly correlated with age (p = 0.002, r = 0.007) and PLT count (p < 0001, r = 0.028) in both groups (Table 2).

3.3. Associations between PDGF-BB, routine parameters, and fibrosis stages

Univariate analysis showed that the parameters age, ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and total bilirubin were positively associated with fibrosis stage, while PLT count, albumin, HBV DNA, and PDGF-BB were negatively associated with fibrosis stage (Table 3). Multiple ordered logistic regression analysis was then performed with the Ishak fibrosis score as the dependent variable, F≥4 as the reference category, and all parameters above as the explanatory variables. This indicated that PDGF-BB, GGT, and PLT count were independent factors of liver fibrosis stage (Table 4). The presence of significant fibrosis (F≥3) is usually used as a determinant for initiating antiviral therapy; the algorithm of independent factors for significant fibrosis was chosen.

3.4. Diagnostic value of serum PDGF-BB and other models in liver fibrosis

The diagnostic value of serum PDGF-BB in predicting liver fibrosis was further assessed using AUROC analysis. The AUROCs of serum PDGF-BB were 0.560 (95% confidence interval (CI) 0.502–0.617) for F≥2, 0.609 (95% CI 0.556–0.662) for F≥3, and 0.574 (95% CI 0.505–0.644) for F≥4 in the total cohort of CHB patients. These findings are shown in Table 5. Additionally, the algorithms by multiple ordered logistic regression analysis showed AUROCs of 0.675 (95% CI 0.623–0.728) for F≥2, 0.705 (95% CI 0.665–0.756) for F≥3, and 0.739 (95% CI 0.681–0.798) for F≥4 (these data are not shown).

To improve the diagnostic performance of serum PDGF-BB, logistic linear analysis was also performed combining PDGF-BB, GGT, and PLT levels, i.e., the PGT; distinct increases in the resulting AUROCs were found, which became 0.711 (95% CI 0.661–0.761) for F≥2, 0.746 (95% CI 0.699–0.793) for F≥3, and 0.755 (95% CI 0.699–0.812) for F≥4. Furthermore, existing APRI and FIB-4 scores were compared against the PGT score, and they produced similar results

Table 2
Associations between serum PDGF-BB levels and routine parameters

PDGF-BB vs.	Total CHB patients		CHB patients with ALT <ULN	
	r/rho	*p*-Value	*r*/rho	*p*-Value
Age (<30, ≥30)	−0.144	0.002[a]	−0.242	0.007[a]
Sex (female, male)	−0.038	0.417	−0.153	0.092
BMI, kg/m^2	0.023	0.618	0.019	0.833
ALT, U/l	−0.011	0.815	−0.12	0.188
AST, U/l	−0.01	0.833	−0.065	0.479
ALP, U/l	0.001	0.98	0.039	0.687
GGT, U/l	−0.034	0.466	−0.03	0.744
Albumin, g/l	−0.021	0.656	0.07	0.448
TBil, μmol/l	−0.053	0.258	0.087	0.345
Platelet count, ×10^9/l	0.224	<0.001[a]	0.2	0.028[a]
HBV DNA, IU/ml	−0.052	0.264	−0.145	0.111
Fibrosis stage				
F0–1, F2, F3, F4, F≥5	−0.16	0.003		
F0–2, F≥3			−0.25	0.0058

PDGF-BB, platelet-derived growth factor BB; CHB, chronic hepatitis B; ALT, alanine aminotransferase; ULN, upper limit of normal; BMI, body mass index; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; TBil, total bilirubin; HBV, hepatitis B virus.
[a] Significant.

for the AUROCs. The PGT score was calculated using the formula: PGT = 1.951 − (0.003 × PLT) + (0.004 × GGT) − (0.072 × logPDGF-BB).

3.5. Diagnostic value of the PGT score for patients with normal ALT

For the 122 patients with normal ALT, the AUROC of the PGT score for F≥2 was 0.756, whereas it was 0.831 for F≥3 and 0.877 for F≥4. In comparison to the existing scores, the PGT score showed equal efficiency to APRI (0.823) and the FIB-4 score (0.822) for significant fibrosis in patients with normal ALT (Table 5). Furthermore, using cut-off values of 1.05, 1.28, and 1.43 produced a sensitivity of 0.95, 0.76, and 0.52, a specificity of 0.29, 0.83, and 0.95, a PPV of 0.30, 0.90, and 0.79, an NPV of 0.96, 0.60, and 0.86, a positive likelihood ratio of 1.31, 4.40, and 11.25, and a negative likelihood ratio of 4.17, 3.43, and 1.98, respectively. Using cut-offs of 1.05 and 1.43 for the absence or presence of significant fibrosis in CHB patients with normal ALT, respectively, the correct diagnosis rate was up to 88.4%; however, patients with PGT within the range of 1.05 to 1.43 still required a liver biopsy for further fibrosis assessment. Additionally, in the 303 patients with ALT levels lower than two times the upper limit of normal (2 × ULN), the AUROC of the PGT score for F≥2 was 0.727, whereas it was 0.775 for F≥3 and 0.746 for F≥4. The existing APRI and FIB-4 scores showed AUROCs of 0.748, 0.788, and 0.757 (APRI) and 0.656, 0.734, and 0.678 (FIB-4) for mild, significant, and severe fibrosis, respectively, in patients with ALT levels lower than 2 × ULN (data not shown).

4. Discussion

PDGF comprises a series of secretory growth factors that play important roles in the pathogenesis of fibrosis. PDGF-BB activates HSCs and induces portal fibroblast proliferation, in addition to regulating chemotaxis, cell migration, and cell survival.[15] In the liver, PDGF-BB levels have been shown to correlate with the incidence of hepatic fibrosis of different etiologies.[13,18,19] However, although numerous studies have evaluated PDGF-BB levels in liver tissue samples obtained from HBV-infected patients and in animal models, few studies have assessed serum PDGF-BB levels in patients with CHB infections. The current study, performed in a

Table 3
Associations between PDGF-BB, routine parameters, and fibrosis stages—univariate analysis[a]

Parameters	F0–1	F2	F3	F≥4	*p*-Value
Age ≥30 years	49 (33.1%)	28 (18.7%)	12 (13.3%)	8 (10.4%)	<0.001
Sex, male	114 (77.0%)	117 (78.0%)	65 (72.2%)	67 (87%)	0.139
BMI, kg/m^2	22.83 ± 2.48	23.47 ± 4.43	23.45 ± 2.92	23.90 ± 2.89	0.052
ALT, U/l	73.43 ± 85.02	122.68 ± 142.35	120.43 ± 179.99	123.63 ± 195.14	0.001
AST, U/l	43.93 ± 40.78	73.87 ± 79.26	89.82 ± 130.16	80.51 ± 110.99	<0.001
ALP, U/l	78.71 ± 25.30	79.74 ± 24.95	90.64 ± 35.33	94.53 ± 29.70	<0.001
GGT, U/l	35.75 ± 40.03	54.97 ± 64.12	69.19 ± 62.72	85.69 ± 80.67	<0.001
Albumin, g/l	45.42 ± 5.24	44.56 ± 4.50	43.33 ± 5.87	42.67 ± 5.99	0.003
TBil, μmol/l	16.35 ± 20.91	16.18 ± 15.40	17.00 ± 9.68	19.17 ± 10.17	0.001
Platelet count, ×10^9/l	193.34 ± 54.75	184.53 ± 54.62	153.33 ± 48.91	140.62 ± 50.39	<0.001
HBV DNA, $\log_{10}$ IU/ml	6.82 ± 1.97	6.16 ± 1.86	6.01 ± 1.66	5.74 ± 1.97	0.001
PDGF-BB, $\log_{10}$ pg/ml	4.70 ± 0.48	4.69 ± 0.46	4.56 ± 0.51	4.31 ± 0.72	0.002
PT, s	13.44 ± 10.62	13.28 ± 6.49	13.39 ± 1.49	13.28 ± 1.99	0.997
INR	1.21 ± 2.32	1.14 ± 1.39	1.08 ± 0.14	1.10 ± 0.14	0.903

PDGF-BB, platelet-derived growth factor BB; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; TBil, total bilirubin; HBV, hepatitis B virus; PT, prothrombin time; INR; international normalized ratio.
[a] Results are presented as the mean ± standard deviation, or *n* (%).

Table 4
Multiple ordered logistic regression analysis with Ishak fibrosis stages as the dependent variable[a]

Fibrosis stage	Multiple analysis	PDGF-BB (log pg/ml)	Platelet count (×10^9/l)	GGT (U/l)
F0–1	OR (95% CI)	2.130 (0.886–5.124)	1.014 (1.002–1.026)	0.982 (0.973–0.991)
	p-Value	0.091	0.019	<0.001
	β	0.751	0.014	−0.018
F2	OR (95% CI)	2.587 (1.090–6.139)	1.010 (0.999–1.022)	0.992 (0.986–0.999)
	p-Value	0.031	0.076	0.028
	β	0.951	0.01	−0.008
F3	OR (95% CI)	3.249 (1.261–8.374)	0.993 (0.981–1.005)	0.998 (0.992–1.005)
	p-Value	0.015	0.261	0.656
	β	1.178	−0.007	−0.002

PDGF-BB, platelet-derived growth factor BB; GGT, gamma-glutamyl transpeptidase; OR, odds ratio; CI, confidence interval.
[a] F≥4 as the reference category.

Table 5
Receiver operating characteristic curve analysis of fibrosis scores in different fibrosis groups; AUROC (95% confidence interval)

	F0–1 vs. F2–6	F0–2 vs. F3–6	F0–3 vs. F4–6
For all patients (n = 465)			
PDGF-BB	0.560 (0.502–0.617)	0.609 (0.556–0.662)	0.574 (0.505–0.644)
PGT score	0.711 (0.661–0.761)	0.746 (0.699–0.793)	0.755 (0.699–0.812)
APRI	0.724 (0.673–0.776)	0.697 (0.649–0.745)	0.684 (0.625–0.743)
FIB-4	0.648 (0.596–0.700)	0.694 (0.643–0.746)	0.654 (0.587–0.721)
For patients with normal ALT levels (n = 122)			
PDGF-BB	0.605 (0.502–0.708)	0.661 (0.556–0.765)	0.549 (0.407–0.691)
PGT score	0.756 (0.668–0.845)	0.831 (0.738–0.925)	0.877 (0.794–0.960)
APRI	0.806 (0.728–0.883)	0.823 (0.732–0.914)	0.884 (0.811–0.957)
FIB-4	0.790 (0.708–0.870)	0.822 (0.740–0.903)	0.791 (0.699–0.882)

AUROC, area under the receiver operating characteristics curve; PDGF-BB, platelet-derived growth factor BB; PGT score, combination of PDGF-BB, gamma-glutamyl transpeptidase, and platelet levels; APRI, aspartate aminotransferase-to-platelet ratio; FIB-4, fibrosis index based on four factors; ALT, alanine aminotransferase.

large cohort, found that serum PDGF-BB levels decreased as fibrosis stage increased (p = 0.003, Spearman's rho = −0.16).

PDGF-BB is typically secreted by a variety of cell types, including PLTs, fibroblasts, endothelial cells, mast cells, and macrophages.[20] There is currently no clear evidence to indicate the types of cells that predominantly express PDGF-BB during hepatic fibrogenesis. In earlier studies, Pinzani et al.[19] and Ikura et al.[13] reported that PDGF-BB mRNA expression was markedly elevated in cirrhotic liver tissues and that infiltrating macrophages and HSCs are the primary sources of PDGF-BB via autocrine or paracrine signaling. From the intrahepatic perspective, PDGF-mediated signaling through PDGFRα or PDGFβ receptors strongly promotes HSC activation and induces phenotypic changes, followed by collagen deposition and fibrogenesis.[21] From the extrahepatic perspective, there are additional underlying cellular events that induce the progression of fibrotic disease. Notably, PLTs are a rich source of PDGF proteins.[22] Yoshida et al. recently confirmed that serum PDGF-BB is largely supplied to damaged liver tissues via PLTs, rather than being produced by resident cells, such as macrophages and activated cholangiocytes.[18] These findings were demonstrated in anti-PLT experiments in which reduced serum and hepatic PDGF-BB levels corresponded to significantly attenuated fibrosis status. The destruction of PLTs is a common complication of chronic liver disease, especially in the case of cirrhosis, and this destruction has been attributed to multiple mechanisms.[23]

In the current study, serum PLT levels were significantly decreased in all HBV-infected patients assessed with fibrosis stage ≥2 (data not shown), and the serum PLT level was highly correlated with the serum PDGF-BB level (Table 2). These results are consistent with those reported previously.[18,24] The results may be explained by the hypothesis that decreases in PLT levels profoundly affect extrahepatic PDGF-BB levels in patients with liver fibrogenesis caused by HBV infection, despite intrahepatic PDGF being expressed by pro-fibrogenic cells, including macrophages and HSCs in the injured liver. Further studies are necessary to explore the mechanisms underlying these relationships.

Serum ALT is the most widely used index to screen for and assess injury status in patients with liver disease. However, the connection between ALT and degree of hepatic injury is not strong, as exemplified by the common observation that a portion of chronic HBV-infected patients, who are categorized as chronic HBV carriers by current diagnostic standards, have serious liver injury despite normal ALT levels.[25]

According to current guidelines, CHB patients with significant fibrosis (Ishak score F≥3) should be treated immediately.[26] In the current study, 26.2% of the 122 patients enrolled with normal ALT levels had significant fibrosis. Thus, serum PDGF-BB levels were compared with the fibrosis stages in patients with normal ALT. In all of the patients evaluated with normal ALT, serum PDGF-BB correlated significantly with fibrosis stage (F0–2 vs. F≥3, p = 0.007) (Figure 1B). Therefore, the data suggest that PDGF-BB could be a potential biomarker for the assessment of fibrosis stage in patients with CHB.

In recent years, several serum biomarkers and marker panels have been developed to predict hepatic fibrosis. Two commonly used scores, APRI and FIB-4, have successfully predicted hepatic fibrosis in large cohorts of HCV-infected patients.[27,28] Numerous reports have also indicated that APRI and FIB-4 scores are useful in clinical practice for assessing liver fibrosis in CHB patients.[9,10,29] The present study showed that the combined evaluation of serum PDGF-BB, GGT, and PLT levels, via PGT score, produced significantly higher AUROCs than serum PDGF-BB alone for diagnosing the different stages of fibrosis. APRI and FIB-4 scores were employed to evaluate significant fibrosis and showed AUROCs of 0.823 and 0.821 in patients with normal ALT levels. Compared to these scores, the use of the PGT score produced similar AUROCs in diagnosing significant fibrosis in patients with normal ALT levels. Moreover, 88.4% of patients would be correctly diagnosed using the cut-offs of 1.05 and 1.43 for the absence or presence of significant fibrosis, respectively, in CHB patients with normal ALT levels.

This study had some limitations. First, it was a cross-sectional study and the authors did not have access to longitudinal data to verify the results. Second, a mechanism for investigating cellular sources of PDGF-BB expression in liver tissue is lacking. Finally, serum PDGF-BB and the PGT score provide robust data, especially in total CHB patients. Additional studies are needed to investigate the use of PDGF-BB and the PGT score for staging liver fibrosis in combination with other fibrosis markers. Therefore, future prospective studies should be performed to reach a higher diagnostic accuracy, especially in differentiating significant/severe fibrosis from moderate stages of fibrosis.

In conclusion, serum PDGF-BB levels decreased remarkably during fibrogenesis and these could be used as a non-invasive biomarker of fibrosis stage in patients with CHB. Furthermore, the PGT score showed equal efficiency to other fibrosis scores in diagnosing significant fibrosis in patients with normal ALT.

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Ethical approval: This study was approved by the local ethics committee of Peking University First Hospital. The complete protocol for the clinical trial has been registered at clinicaltrials.gov (NCT01962155) and chictr.org (ChiCTR-DDT-13003724).

Conflict of interest: No conflicts of interest are declared by any of the authors.

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